

development of a complex vascular microarchitecture in a physiological microdevice to study the impact of a tumoral context on the brain angiogenesis and blood-brain barrier

Thomas Sivier^{1,*}, M. Gourgues¹, F. Chollet¹, V. Humblot¹, T. Leblois¹, Agathe Figarol¹

¹ *Université Marie et Louis Pasteur, CNRS, institut FEMTO-ST, F-25000 Besançon, France*

*Correspondance: thomas.sivier@femto-st.fr

The blood-brain barrier (BBB) strictly controls exchanges between the blood and the brain to block most external aggressions. However, glioblastoma multiforme, the most common and aggressive primary brain cancer, modifies its microenvironment and the BBB with an uncertain evolution. Organs-on-chips are innovative biotechnological tools that reproduce an organ in vitro, helping to understand many pathological mechanisms. Developing a BBB-on-chip (BBBoC) model is particularly relevant to compare function in healthy and tumoral contexts.

An initial BBBoC model was constructed with a straight hollow channel surrounded by a hydrogel matrix containing cancer and supporting cells: astrocytes and pericytes. This channel, seeded with endothelial cells, acts as an arteriole when perfused with nutritive medium mimicking blood flow. To bring the model closer to physiological reality, complexifying the channel design is required. Several sacrificial materials were compared as templates for complex channels: carbohydrate glass, gelatin, and mixed waxes. They were evaluated regarding synthesis, molding, demolding (in a PDMS mold from 3D-printing), shape retention, and dissolution, while considering cell preservation. Biocompatibility was assessed on glioblastoma (U87-MG) and brain endothelial cells (HBMEC), astrocytes and pericytes using live-dead kit. Gelatin appeared to be the optimal choice for the BBBoC model. Its dissolution with albumin generates a complex channel network.

Capillarization assays are underway to evaluate endothelial cell organization in the channels, with emphasis on tight junctions. In parallel, different hydrogel compositions using hyaluronic acid are being tested. A dedicated chip-holding device was developed to enhance reproducibility. Model integrity will be validated using fluorescent dextran and nanoparticles before introducing cancer cells. In the longer term, this system could become an innovative tool for disease modeling and drug screening.

References:

- [1] Zhou, S. (2023). *Blood-brain barrier on-a-chip and its application. Theoretical and Natural Science*, 8(1), 284-289. doi:10.54254/2753-8818/8/20240433.
- [2] Liu, S., Wang, T., Li, S., & Wang, X. (2022). *Application status of sacrificial biomaterials in 3D bioprinting. Polymers*, 14(11), 2182. doi:10.3390/polym14112182.
- [3] Cui, B., & Cho, S.-W. (2022). *Blood-brain barrier-on-a-chip for brain disease modeling and drug testing. BMB Reports*, 55(5), 213-219. doi:10.5483/BMBRep.2022.55.5.043.